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Localization of a gene for non-syndromic hearing loss (DFNA5) to chromosome 7p15

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Progressive hearing loss affects approximately 50% of the elderly by the age of 80, and is most likely caused by an interaction of genetic and environmental factors. Identification of the genes responsible for hereditary hearing loss is therefore important. Families with pure genetic degenerative hearing disorders may be helpful as the same genes may be also involved in age-related hearing loss in general. In this study we have performed a genome search in an extended Dutch family with autosomal dominant progressive hearing loss starting in the high frequencies. The gene causing hearing loss in this family was localized to the short arm of chromosome 7, in a 15 cM interval between markers D7S493 and D7S632.

INTRODUCTION

Hearing impairment is one of the most frequent handicaps in the Western world. Two groups can be distinguished: pre-lingual and post-lingual hearing loss. Approximately 1/1000 children is born deaf. About half of these cases is caused by genetic factors, which makes pre-lingual deafness one of the most frequent genetic conditions (1–3). However, only a small part of hearing loss in the total population is due to pre-lingual deafness, and the percentage of adults with a hearing impairment increases significantly with age. Hearing loss of more than 25 dB is present in approximately 1% of young adults between 18 and 24 years, in approximately 10% of the individuals between 55 and 64, and in approximately 50% of the elderly between 75 and 80 (3).

The causes of progressive hearing loss starting in adulthood are unknown in most cases. In many instances, this type of progressive hearing impairment is most likely caused by an interaction of different genes and environmental factors. A single cause can be identified only in a minority of cases. In some patients a specific environmental factor such as noise, trauma, infection or an ototoxic drug is known to be responsible for the hearing loss. On the other hand, a number of families have been reported with a clear autosomal dominant progress-

ive hearing loss (4). In some of these families, hearing impairment is present in many family members, thereby facilitating gene localization studies by linkage analysis. These families present a unique opportunity for the identification of genes involved in progressive hearing loss. The same genes may be involved in both pure genetic hearing loss and hearing deterioration due to a combination of genetic and environmental factors. An example of such a gene is the mitochondrial ribosomal RNA gene, for which it is known that the same mutation gives rise to familial susceptibility to aminoglycoside-induced deafness in some families, and non-syndromic pre-lingual deafness in another family (5). In time, the identification of genes for pure genetic progressive hearing loss will lead to a better insight into the mechanisms causing hearing deterioration in general. These mechanisms may provide a useful model for certain types of age-related hearing loss.

Many studies on the etiology of pre-lingual hearing loss have been carried out. More than 70% of pre-lingual hereditary deafness is non-syndromic, and not associated with any other clinical abnormality (1,6). Non-syndromic pre-lingual hearing loss is genetically heterogeneous and it has been estimated that more than 100 genes might be involved (7). Approximately 75% of pre-lingual deafness has an autosomal recessive mode of inheritance, and only about 25% an autosomal dominant mode of transmission (1). No comparable data are available for post-lingual hereditary hearing loss, and its frequency and mode of inheritance are inadequately known.

No gene has been identified yet for hereditary hearing loss, but the number of genes that have been localized has increased rapidly over the last year. The first gene, DFNA1, was localized to chromosome 5 in 1992 (8). In 1994 and 1995, five additional genes were assigned to chromosome 1 (DFNA2) (9), chromosome 19 (DFNA4) (10), chromosome 13 (DFNB1 and DFNA3) (11,12), chromosome 11 (DFNB2) (13), and chromosome 17 (DFNB3) (14), respectively.

In this study we have performed a gene localization in an extended Dutch family with autosomal dominant progressive hearing loss, starting in the high frequencies. After exclusion of linkage to known loci for hereditary hearing loss, this new locus (DFNA5) was localized to chromosome 7p.

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RESULTS

Family pedigree

In 1966, 1972 and 1983 an extended Dutch family with hereditary hearing loss was described by Huizing *et al.* (15–20). The family comprises five generations affected by progressive sensorineural hearing loss beginning in the high frequencies. The pattern of inheritance is autosomal dominant with complete penetrance. At the last follow-up study, 104 descendants were found to be affected (18–20). No associated abnormalities were found in this family, indicating that the hearing loss is non-syndromic. The age of onset of the hearing loss is between 5–15 years. In the early phases of hearing deterioration, high frequency sensitivity is lost with thresholds dropping to 80 dB above 1000 Hz, while hearing at lower frequencies still remains normal. With increasing age and progressive high tone loss, the low frequencies become

affected. Around the age of 40–50 years, the low frequencies are also severely impaired. Vestibular functions are not affected and there are no complaints of tinnitus.

Genome search

Linkage to the five published loci for non-syndromic hearing loss was investigated in a first attempt to localize the gene. The loci on chromosome 5 (DFNA1) and chromosome 1 (DFNA2) had been excluded previously (9). To exclude the other four loci, DFNA4, DFNB1, DFNB2 and DFNB3, respectively, genetic markers flanking these loci were analyzed. Each of these four loci could be excluded with lod scores below –2 over the complete candidate region (results not shown).

To perform a genome search, a subset of 31 family members was selected that gave conclusive lod scores in simulated linkage analysis using the computer program SLINK (21). A genome search using a set of polymorphic simple tandem repeats covering the complete genome (22) was initiated. A total of 111 markers, which excluded 51% of the genome, were analyzed before a marker was found that gave a positive lod score above +3. With marker D7S513, a maximum lod score of 4.94 at 0% recombination was obtained.

Linkage to chromosome 7p

Marker D7S513 was subsequently typed on all the other family members that were not part of the initial subset used in the genome search. The total pedigree that was used for the linkage analysis is shown in Figure 1. Sixteen additional markers spanning a large region around D7S513, were subsequently analyzed. Two-point lod scores were calculated for all markers (Table 1). Their position on the Génethon genetic map (23) is shown in Figure 2. Positive lod scores above +3 were present for markers from a broad region. For markers D7S629, D7S682, D7S673, D7S529 and D7S516, maximum lod scores of 7.00, 7.98, 13.53, 4.47 and 10.07 respectively were obtained at 0% recombination, indicating that these markers are closely linked to DFNA5.

The most likely haplotype for all 17 markers analyzed (Table 1) was constructed. No evidence for non-penetrance or

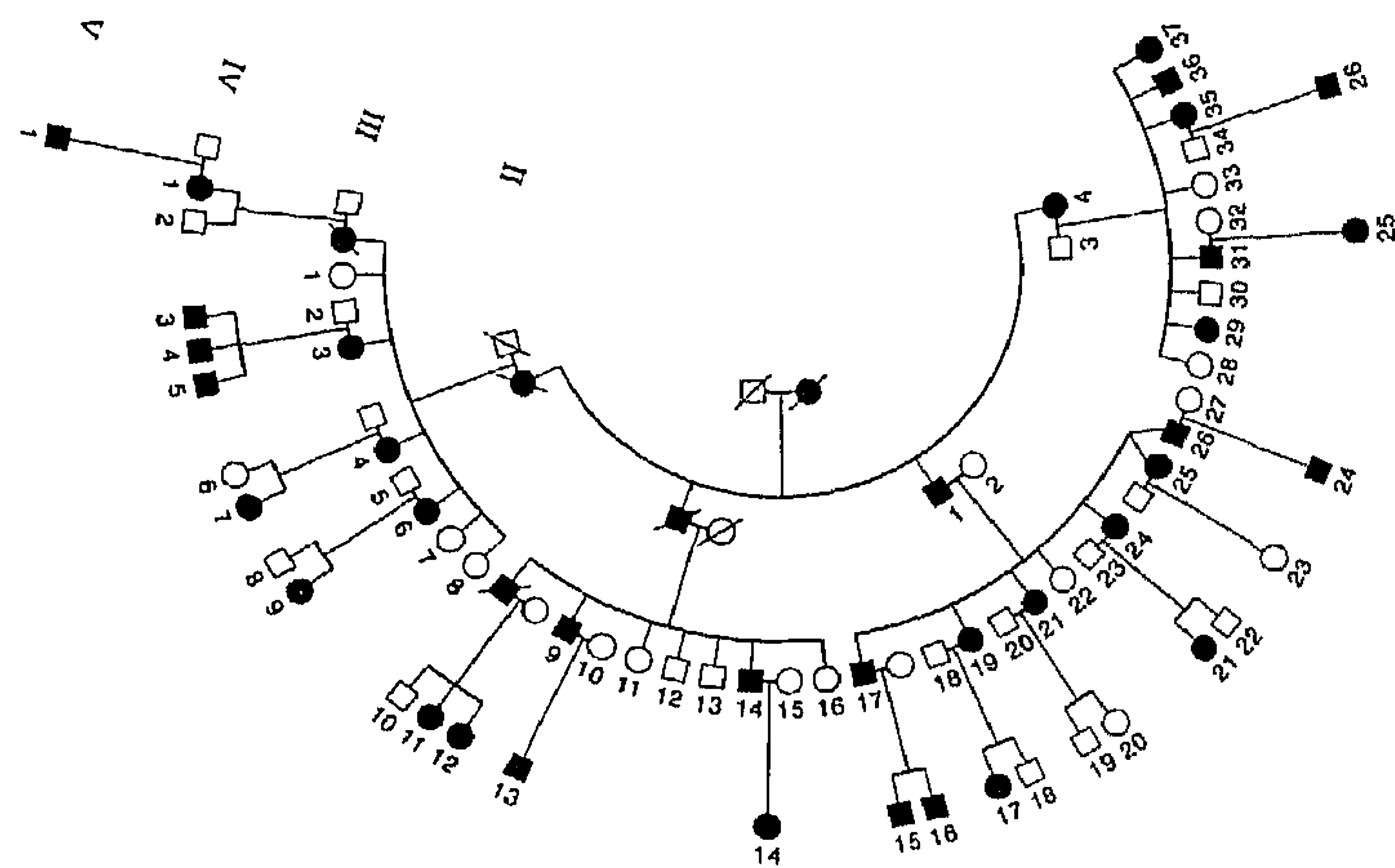


Figure 1. Part of the pedigree with autosomal dominant hearing loss that was used for linkage analysis. Only family members whose DNA was studied, are numbered. Individuals necessary to reconstruct the pedigree are shown without number. Affected individuals are represented by solid symbols.

Table 1. Two-point lod scores between hearing loss and chromosome 7 markers

Locus	Recombination fraction (θ)							Z_{\max}	(θ)
	0.00	0.01	0.05	0.10	0.20	0.30	0.40		
D7S517	–6.93	–3.49	–0.44	1.00	1.80	1.50	0.63	1.81	(0.21)
D7S513	3.54	4.37	5.76	6.13	5.49	4.01	1.96	6.13	(0.10)
D7S664	4.99	5.42	6.04	6.01	5.05	3.50	1.59	6.09	(0.07)
D7S507	7.07	7.55	8.16	8.00	6.71	4.75	2.30	8.18	(0.06)
D7S503	6.35	7.12	7.93	7.83	6.58	4.65	2.24	7.96	(0.06)
D7S488	4.41	4.78	5.29	5.24	4.43	3.15	1.55	5.32	(0.06)
D7S654	0.79	0.84	0.96	0.97	0.83	0.60	0.31	0.97	(0.08)
D7S493	8.13	8.14	7.86	7.26	5.74	3.94	1.86	8.14	(0.01)
D7S629	7.00	6.88	6.40	5.77	4.43	2.99	1.43	7.00	(0.00)
D7S682	7.98	7.85	7.33	6.65	5.20	3.57	1.76	7.98	(0.00)
D7S673	13.53	13.33	12.43	11.27	8.77	5.98	2.85	13.53	(0.00)
D7S529	4.47	4.39	4.05	3.61	2.70	1.72	0.71	4.47	(0.00)
D7S516	10.07	9.91	9.26	8.40	6.57	4.55	2.28	10.07	(0.00)
D7S632	4.87	5.14	5.49	5.37	4.43	3.03	1.32	5.50	(0.06)
D7S526	0.49	2.55	4.33	4.87	4.51	3.30	1.59	4.90	(0.11)
D7S690	–0.18	0.36	1.37	1.79	1.79	1.34	0.64	1.88	(0.15)
D7S683	–3.57	–2.49	–0.76	0.08	0.63	0.60	0.30	0.67	(0.24)

phenocopies was present. Informative crossovers defining the interval containing DFNA5 were identified. Several recombinations with the seven most telomeric markers (D7S517–D7S654)

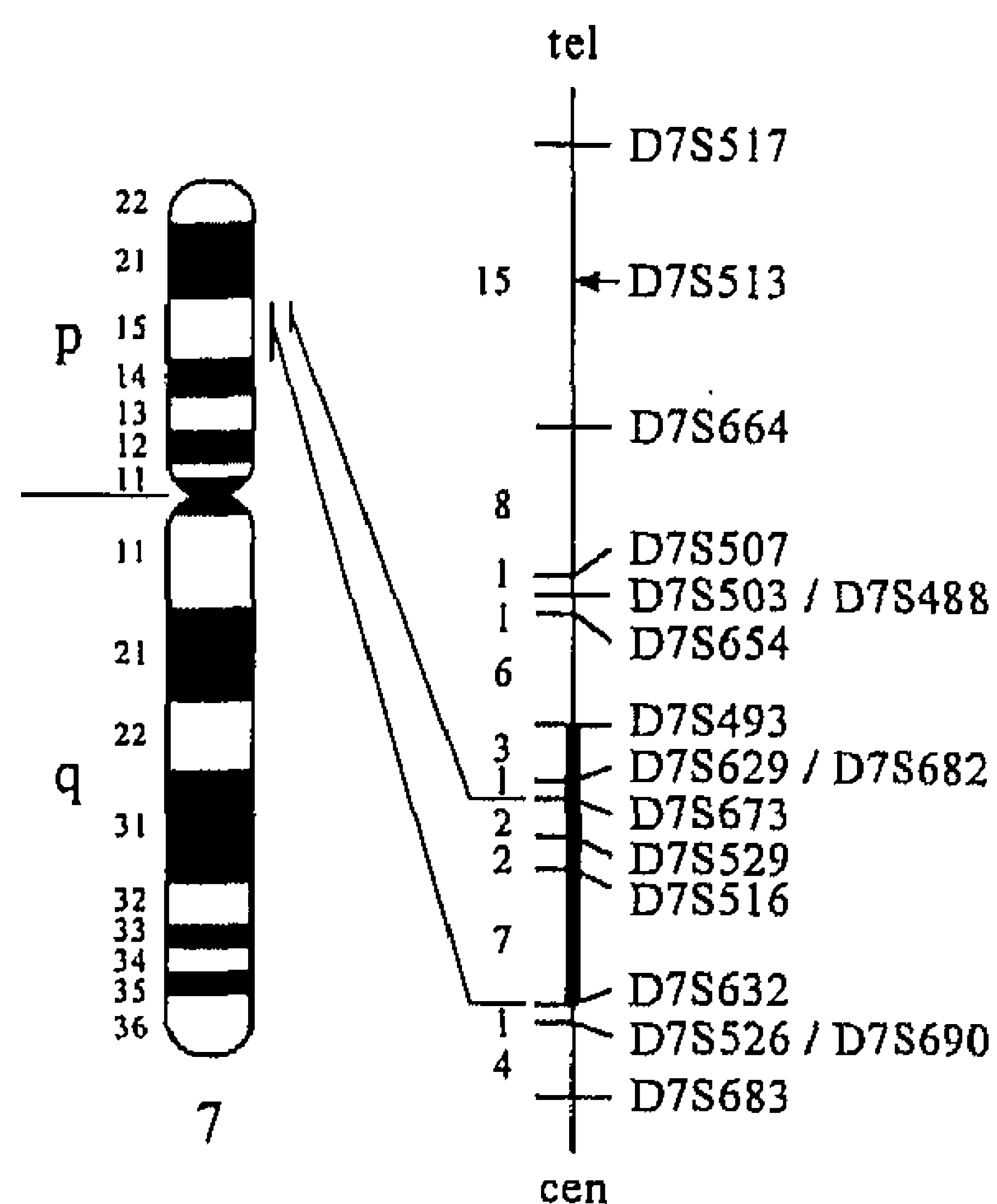


Figure 2. Genetic map of the region surrounding DFNA5. The genetic map was obtained from Génethon (23). Marker D7S513 is not present on the Génethon map, but is located between D7S517 and D7S664, according to the Cooperative Human Linkage Center (CHLC) map (33). Markers D7S673 and D7S632 have been mapped to chromosome band 7p15 by *in situ* hybridization (34). Genetic distances between markers are indicated in cM next to the map.

were found, localizing DFNA5 centromeric to these markers. A single informative crossover with D7S493 is present in patient IV-16, placing DFNA5 centromeric to this marker. No recombination was observed with D7S629, D7S682, D7S673, D7S529 and D7S516. One informative crossover in affected individual III-4, and three informative crossovers in unaffected individuals III-7, III-33, and IV-18 are present with D7S632, placing DFNA5 telomeric to this marker. This was confirmed by the finding of several recombinations with each of the three most centromeric markers D7S526, D7S690 and D7S683. A graphical representation of the key recombinations with the most closely linked markers is presented in Figure 3. The key recombinations indicate that the gene for hearing loss is most likely located in a 15 cM region between D7S493 and D7S632.

DISCUSSION

The Dutch family with hereditary hearing loss that was investigated in this study is one of the largest families with hereditary hearing loss ever reported with more than 100 affected patients (15–20). For many years this family has been a reference family for autosomal dominant hearing loss of the high frequencies in the Mendelian Inheritance in Man catalogue (MIM 124800) (4).

We performed a genome search to localize the gene responsible for hearing loss, and found linkage with markers located on chromosome 7p. A region of 15 cM was defined between

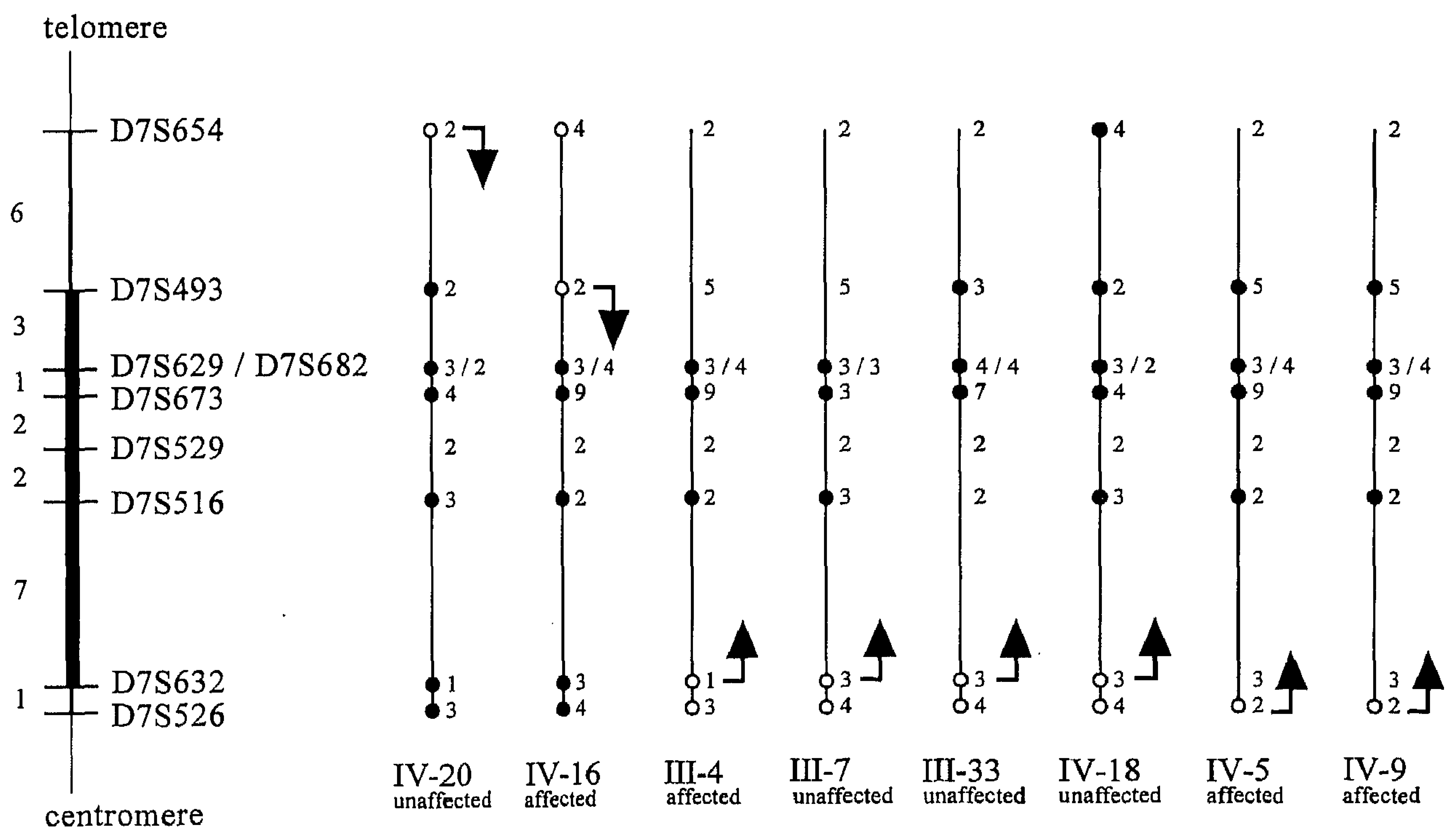


Figure 3. Key recombinations between DFNA5 and chromosome 7 markers. The most important recombinational events between DFNA5 and 9 chromosome 7p markers from the DFNA5 region are given as haplotypes next to the genetic map. Genetic distances between markers are given in cM. For each haplotype informative alleles are indicated by circles: black circles indicate chromosomal regions that contain DFNA5, and open circles indicate chromosomal regions from which DFNA5 is excluded. Allele numbers without circle are uninformative. The localization of DFNA5 by each recombinant is indicated by an arrow. The pedigree number and affection status is given below each haplotype. In conclusion, the key crossovers indicate that DFNA5 is most likely located in a 15 cM region between markers D7S493 and D7S632.

markers D7S493 and D7S632 that most likely contains the gene responsible for hearing loss (DFNA5) in this family. A candidate region of 15 cM seems large for a family comprising more than 50 meiotic events. This is mainly the consequence of the limited number of markers that are available in this region, and the fact that some of these markers were hardly informative in the key recombinants (Fig. 3). The availability of new informative markers will most likely reduce the candidate region further.

The genes for two autosomal dominant progressive degenerative eye diseases, degenerative cystoid macular dystrophy (DCMD) and a form of retinitis pigmentosa (RP9) have been mapped to regions that overlap with the candidate region for DFNA5 (24,25). It must be noted that Usher syndrome, a syndromic form of hereditary hearing loss, is characterized by a combination of hearing loss and retinitis pigmentosa. In addition, a locus for non-syndromic deafness on chromosome 11 (DFNB2) is localized to the same region as a form of Usher syndrome (13). Although it is theoretically possible that DFNA5, RP9, and DCMD are caused by different mutations in the same gene, it is perhaps more likely that these three genes map to the same interval by chance. Amphiphysin (AMPH), a protein peripherally associated with synaptic vesicles (26), has been suggested as a candidate gene for RP9 and DCMD as it has been mapped to this region by FISH (26). However, as a more precise localization of AMPH is lacking, it remains unknown whether AMPH is located in the candidate region of RP9, DCMD or DFNA5. A number of other genes are located in 7p15 (4), including aquaporin (AQP1), a water selective transmembrane channel (27). However, the precise genetic localization of AQP1 proximal of D7S632 (28) excludes this gene as a candidate gene for DFNA5.

It is widely believed that there is a lack of suitable families with hereditary deafness in the Western world, as deaf individuals very frequently intermarry in the Western world. This assortative mating introduces several deafness genes into one family, thereby impairing gene localization studies. However, for dominant progressive hearing loss there is no assortative mating because significant hearing loss is only present in mid-life. Large families of this type have been described in countries all over the world, including the Western world. It is our personal experience that this type of hereditary hearing loss is even more frequent than can be estimated from the literature, and might be the most frequent form of genetic hearing impairment. Therefore, extended families with dominant progressive hearing loss form an excellent opportunity to identify genes causing hearing loss. Further study of these genes can provide more insight in the process of progressive hearing loss, and may be important for an understanding of the very frequent hearing loss in adulthood.

MATERIALS AND METHODS

Family data

Part of the family was restudied at the time of blood sampling for the linkage analysis. Otoscopic and audiometric examinations were performed on 88 family members. Pure tone audiometry was performed at 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz for air conduction, and at 500, 1000, 2000 and 4000 Hz for bone conduction. In addition, clinical data and audiograms from all previous examinations were reanalyzed. Family members with a typical bilateral sensorineural hearing loss of the high tones below the 95th percentile of an age and sex-dependent control audiometric curve (29) were

considered to be affected. Family members over the age of 15 were considered to be unaffected if the hearing thresholds at all frequencies were better than the 50th percentile of the age-dependent control curve. Individuals at risk under the age of 15, persons with hearing loss suspected to be due to non-genetic causes, or family members with a conductive hearing loss or an audiometric curve atypical for the family, were excluded from the linkage analysis. In total, linkage analysis was performed on 68 family members, including 36 affected patients.

Genetic analysis

Genomic DNA was extracted by standard techniques. Markers not present in the fluorescent mapping panel (22) were analyzed radioactively using standard procedures (30). For the genome search, simple tandem repeat polymorphisms were amplified using a fluorescently labeled primer and analyzed on an Applied Biosystems (ABI) DNA sequencer model 373A as described previously (22).

Fragment sizes of the marker alleles were calculated using the GENESCAN 672 (version 1.2, ABI) software. Data were subsequently exported to the GENOTYPER (version 1.1, ABI) software package. A table containing the allele fragment sizes was exported from GENOTYPER as a text file. The data were further handled using the GENOME SEARCHER computer program (Van Camp *et al.*, unpublished). GENOME SEARCHER was used as an interface between GENOTYPER, the LINKAGE and FASTLINK computer programs (31,32), and a commercial computer program for pedigree drawing (CYRILLIC, Cherwell Scientific).

Linkage parameters

Linkage analysis was performed using the software package LINKAGE version 5.1. (31), and the FASTLINK computer program (32). The gene frequency for hearing loss due to mutations in this gene was set at 0.0001. For progressive hearing loss with adult onset, the clinical diagnosis causes specific problems. As hearing loss is frequent in the general population, non-gene carrying family members may be present with a hearing impairment that cannot be distinguished from gene-carrying family members, giving rise to phenocopies. Also certain gene-carrying individuals may only be mildly affected and may incorrectly be diagnosed as unaffected, giving rise to non-penetrance. It is our personal experience that phenocopies and non-penetrance occasionally occur in families with progressive hearing loss. Therefore, penetrance was arbitrarily set at 98% for heterozygotes to allow for non-penetrance, and 2% for normal homozygotes to allow for possible phenocopies. Recombination frequencies were assumed to be equal for males and females. Allele frequencies were set equal to each other.

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